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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JANSSENS, Frans, Eduard [BE/BE]; Tinstraat 79, B-2820 Bonheiden (BE). LEENAERTS, Joseph, Elisabeth [BE/BE]; Potbergstraat 35, B-2310 Rijkevorsel (BE). VAN ROOSBROECK, Yves, Emiel, Maria [BE/BE]; Zonderschotsesteenweg 26, B-2220 Heist-op den-Berg (BE).

(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

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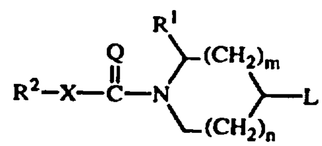
(54) Title: 1-(1,2-DISUBSTITUTED PIPERIDINYL)-4-(FUSED IMIDAZOLE)-PIPERIDINE DERIVATIVES

(57) Abstract

This invention concerns the compounds of formula (I), the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein n is 0, 1 or 2; m is 1 or 2, provided that if m is 2, then n is 1; =Q is =O or $=NR^3$; X is a covalent bond or -O-, -S-, $-NR^3-$; R^1 is Ar^1, Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, wherein each C_{1-6}alkyl group is optionally substituted; R^2 is Ar^2, Ar^2C_{1-6}alkyl, Het or HetC_{1-6}alkyl; R^3 is hydrogen or C_{1-6}alkyl; L is a piperidine derivative of formula (a-1) or a spiro piperidine derivative of formula (a-2); Ar^1 is phenyl or substituted phenyl; Ar^2 is naphtalenyl; phenyl or substituted phenyl; and Het is a monocyclic or bicyclic heterocycle; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom; as substance P antagonists; their preparation, compositions containing them and their use as a medicine.



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1-(1,2-DISUBSTITUTED PIPERIDINYL)-4-(FUSED IMIDAZOLE)-PIPERIDINE DERIVATIVES

This invention concerns novel 1-(1,2-disubstituted piperidinyl)-4-(fused imidazole) piperidine derivatives having tachykinin antagonistic activity, in particular substance P antagonistic activity, and their preparation; it further relates to compositions comprising them, as well as their use as a medicine.

Substance P is a naturally occurring neuropeptide of the tachykinin family. There are ample studies showing that substance P and other tachykinins are involved in a variety of biological actions, and therefore, play an essential role in various disorders (Regoli et al., Pharmacological Reviews 46(4), 1994, p. 551-599, "Receptors and Antagonists for Substance P and Related Peptides"). The development of tachykinin antagonists has led to date to a series of peptide compounds of which might be anticipated that they are metabolically too labile to be employed as pharmaceutically active substances (Longmore J. et al., DN&P 8(1), February 1995, p. 5-23, "Neurokinin Receptors"). The present invention concerns nonpeptide tachykinin antagonists, in particular nonpeptide substance P antagonists, which in general are metabolically more stable, and hence, may be more appropriate as pharmaceutically active substances.

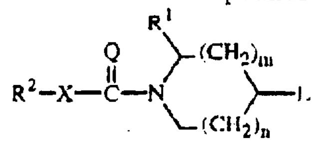
Several nonpeptide tachykinin antagonists are disclosed in the art. For instance, EP-0,532,456-A, published on March 17, 1993, discloses 1-acylpiperidine compounds, in particular 2-arylalkyl-1-arylcarbonyl-4-piperidinamine derivatives, and their use as substance P antagonists.

WO 92/06981, published on April 30, 1992, discloses 11-[4-substituted-(piperidinyl or piperidinylidene)]-imidazobenzazepines as agents useful in the treatment of asthma and other allergic diseases and in the treatment of inflammation. WO 92/22553, published on December 23, 1992, discloses 10-(piperidinyl or piperidinylidene)-imidazo[1,2-a](pyrrolo, thieno and furano)[3,2-d]azepine derivatives having antiallergic activity. WO-94/13680, published on June 23, 1994, discloses 10-(piperidinyl or piperidinylidene)-imidazo[1,2-a](pyrrolo, thieno and furano)[2,3-d]azepine derivatives having antiallergic activity. Further, WO 95/02600, published on January 26, 1995, discloses other piperidinyl- or piperidinylidene substituted imidazoazepine derivatives also having antiallergic activity.

The present compounds differ from the art compounds in that they invariably contain a 4-substituted-piperidine moiety in the 4-position of a 2-substituted-(piperidine- or

homopiperidine) group or in the 3-position of a 2-substituted-pyrrolidine group, and by their favourable farmacological properties.

Hence, the present invention concerns novel compounds of formula



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

m is 1 or 2, provided that if m is 2, then n is 1;

=Q is =O or =NR^3;

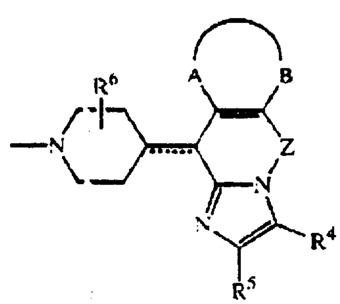
X is a covalent bond or a bivalent radical of formula -O-, -S-, -NR^3-;

R^1 is Ar^1, Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, wherein each C_{1-6}alkyl group is optionally substituted with hydroxy, C_{1-4}alkyloxy, oxo or a ketalized oxo substituent of formula -O-CH_2-CH_2-O- or -O-CH_2-CH_2-CH_2-O-;

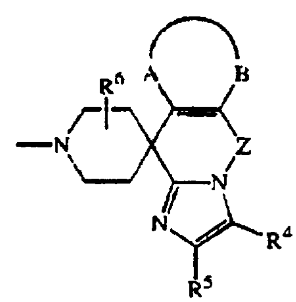
R^2 is Ar^2, Ar^2C_{1-6}alkyl, Het or HetC_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

L is a radical of formula



(a-1) or



(a-2);

wherein the dotted line is an optional bond;

each -A-B- independently is a bivalent radical of formula

-Y-CR^7=CH-	(b-1);
-CH=CR^7-Y-	(b-2);
-CH=CH-CH=CH-	(b-3);
-CH=CR^7-CH=CH-	(b-4);
-CH=CH-CR^7=CH-	(b-5); or
-CH=CH-CH=CR^7-	(b-6);

wherein each Y independently is a bivalent radical of formula -O-, -S- or -NR^8-;

each R^7 independently is C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl;

carboxyl or hydroxycarbonylC_{1-6}alkyl; or

R^7 is hydrogen in case -A-B- is a radical of formula (b-1) or (b-2);

R^8 is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

each Z independently is Z^1 or Z^2;

wherein Z^1 is a bivalent radical of formula $-CH_2-$, $-CH_2-CH_2-$ or $-CH=CH-$; provided that when L is a radical of formula (a-1) and the dotted line is an extra bond, then Z^1 is other than $-CH_2-$;

Z^2 is a bivalent radical of formula $-CH_2-CHOH-$, $-CH_2-O-$, $-CH_2-C(=O)-$ or $-CH_2-C(=NOH)-$, provided that the $-CH_2-$ moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring;

each R^4 independently is hydrogen; C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl or carboxyl;

each R^5 independently is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, Ar^1 or halo; or

R^4 and R^5 taken together may form a bivalent radical of formula $-CH=CH-CH=CH-$ or $-CH_2-CH_2-CH_2-CH_2$;

each R^6 is hydrogen, C_{1-6}alkyl or Ar^1C_{1-6}alkyl;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or haloC_{1-4}alkyloxy;

Ar^2 is naphtalenyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkyloxy, haloC_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl and mono- or di(C_{1-4}alkyl)-aminocarbonyl; and

Het is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl.

The heterocycles in the definition of Het are preferably connected to the rest of the

molecule, *i.e.* X, -C(=Q)- or C_{1-6}alkyl, by a carbon atom.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having form 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like.

As used in the foregoing definitions and hereinafter, haloC_{1-4}alkyl is defined as mono- or polyhalosubstituted C_{1-4}alkyl, in particular C_{1-4}alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. Said salts can conveniently be obtained by treating the base form of the compounds of formula (I) with appropriate acids such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The pharmaceutically acceptable addition salts as mentioned hereinabove are also meant to comprise the therapeutically active non-toxic base, in particular, a metal or amine addition salt forms which the compounds of formula (I) are able to form. Said salts can conveniently be obtained by treating the compounds of formula (I) containing acidic hydrogen atoms with appropriate organic and inorganic bases such as, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

For isolation and purification purposes, it is also possible to use pharmaceutically unacceptable salts. Only the pharmaceutically acceptable, non-toxic salts are used therapeutically and those salts are therefore preferred.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture, more in particular the racemic mixture, of all possible stereochemically and conformationally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration. For the compounds having two or more stereogenic centers, the relative stereodescriptors R* and S* are used in accordance with the Chemical Abstracts rules (Chemical Substance Name Selection Manual (CA), 1982 Edition, Vol. III, Chapter 20). Substituents on bivalent cyclic saturated radicals may have either the *cis*- or *trans*-configuration. More in particular, the substituents R^1 and L are substituted on the nitrogen containing ringsystem in a *cis* or *trans* configuration. For compounds of formula (I) wherein L is a radical of formula (a-1), the substituents R^6, provided it is other than hydrogen, and the fused imidazolyl moiety, provided it is connected to the piperidine ring by a single bond, may be substituted on the piperidine ring in a *cis* or *trans* configuration. The radicals $>C=NR^3$ and C_{3-6}alkenyl may have the E- or Z-configuration. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or mixtures thereof are intended to be embraced within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For instance, compounds of formula (I) wherein X is -NH- and =Q is =O may exist in their corresponding tautomeric form.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the

so-called *N*-oxide, particularly those *N*-oxides wherein a piperidine-nitrogen is *N*-oxidized.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

A special group of compounds are those compounds of formula (I) wherein Het is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl.

A first group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

a) R^1 is Ar^1C_{1-6}alkyl; or

b) R^2 is furanyl; naphtalenyl; quinolinyl; indolyl; pyrazinyl; benzofuranyl; benzothienyl; benzothiazolyl; isoxazolyl; quinoxalinyl; each of said monocyclic or bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl; or R^2 is phenylC_{1-6}alkyl; phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl and haloC_{1-4}alkyl, in particular, selected from methyl and trifluoromethyl; or

c) n is 1; or

d) m is 1; or

e) =Q is =O; or

f) X is a covalent bond or a bivalent radical of formula -O- or $-NR^3-$.

A second group of interesting compounds consists of those compounds of formula (I) wherein L is a radical of formula (a-1), suitably, a radical of formula (a-1) wherein -A-B- is a radical of formula (b-1), (b-2) or (b-3); Z is Z^1; R^4 is hydrogen, formyl or hydroxy-C_{1-6}alkyl; $R^5$is hydrogen; or R^4 and R^5 taken together form a bivalent radical of formula -CH=CH-CH=CH-; R^6 is hydrogen.

A third group of interesting compounds consists of those compounds of formula (I) wherein L is a radical of formula (a-2), suitably, a radical of formula (a-2) wherein -A-B- is a radical of formula (b-3); Z is Z^1; R^4, R^5 and R^6 are hydrogen.

A fourth group of interesting compounds consists of those compounds of formula (I) wherein L is a radical of formula (a-1) wherein -A-B- is a radical of formula (b-1), (b-2),(b-3), (b-5) or (b-6); Z is Z^1 or Z^2; R^4 is hydrogen, halo, C_{1-6}alkyl, formyl, C_{1-6}alkyloxycarbonyl or hydroxyC_{1-6}alkyl; $R^5$is hydrogen, C_{1-6}alkyl or hydroxyC_{1-6}alkyl; or R^4 and R^5 taken together form a bivalent radical of formula -CH=CH-CH=CH-; R^6 is hydrogen.

Of special interest are those compounds of formula (I) wherein R^1 is Ar^1C_{1-6}alkyl, R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl, X is a covalent bond and =Q is =O.

Further of special interest are those compounds of formula (I) wherein n and m are 1.

A particular group of compounds consists of those compounds of formula (I) wherein R^1 is phenylmethyl; R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl; n, m are 1; X is a covalent bond; and =Q is =O.

Another particular group of compounds consists of those compounds of formula (I) wherein L is a radical of formula (a-1) wherein the dotted line is an optional bond; -A-B- is a radical of formula (b-1) wherein Y is -S-; and R^7 is hydrogen; or -A-B- is a radical of formula (b-2) wherein Y is -S- or -NR^8-; and R^7 is hydrogen; or -A-B- is a radical of formula (b-3); Z is Z^1 or Z^2 wherein Z^1 is a bivalent radical of formula -CH_2- or -CH_2-CH_2-, provided that when the dotted line is an extra bond, then Z^1 is other than -CH_2-; and Z^2 is a bivalent radical of formula -CH_2-O-, -CH_2CHOH- or CH_2-C(=O)-, provided that the -CH_2- moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring; R^4 is hydrogen, formyl or hydroxymethyl; R^5 is hydrogen; or R^4 and R^5 taken together form a bivalent radical of formula -CH=CH-CH=CH-; R^6 is hydrogen.

Yet another particular group of compounds consists of those compounds of formula (I) wherein L is a radical of formula (a-2) wherein -A-B- is a radical of formula (b-3); Z is a bivalent radical of formula -CH_2-CH_2-; R^4, R^5 and R^6 are hydrogen.

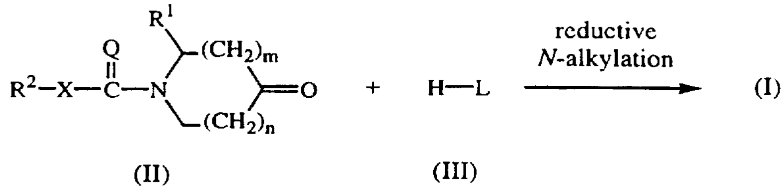
Preferred compounds are those compounds of formula (I) wherein R^1 is phenylmethyl; R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl; n, m are 1; X is a covalent bond;and =Q is =O.

More preferred compounds are those particular groups of compounds wherein R^1 is phenylmethyl; R^2 is phenyl substituted with 2 substituents selected from methyl or

trifluoromethyl; n, m are 1; X is a covalent bond; and =Q is =O.

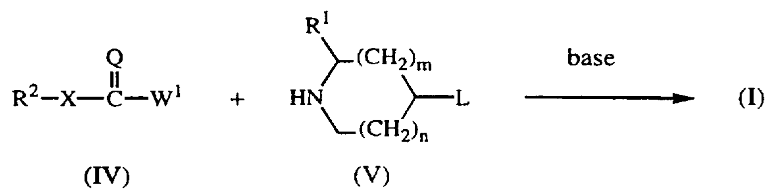
Most preferred are
1-[3,5-bis(trifluoromethyl)benzoyl]-4-(5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidin]-1-yl)-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,9,10-tetrahydro-imidazo[1,2-a]thieno-[2,3-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,7,10-tetrahydro-7-methylimidazo-[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine; and
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(3-formyl-5,6-dihydro-11*H*-imidazo-[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;
4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; and
4-[4-(5,6-dihydro-6-oxo-10*H*-imidazo[1,2-a]thieno[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

The compounds of formula (I) can be prepared by reductively *N*-alkylating an intermediate of formula (III) with an intermediate of formula (II). Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol, toluene or a mixture thereof, and in the presence of a reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride. In case a borohydride is used as a reducing agent, it may be convenient to use a catalyst such as, for example, titanium(IV) isopropylate as described in J. Org. Chem, 1990, *55*, 2552-2554. Using said catalyst may also result in an improved *cis/trans* ratio in favour of the *trans* isomer. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. Stirring and optionally elevated temperatures and/or pressure may enhance the rate of the reaction.



In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

The compounds of formula (I) can also be prepared by reacting an intermediate of formula (IV) wherein W^1 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy, with an intermediate of formula (V). The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between RT and reflux temperature.



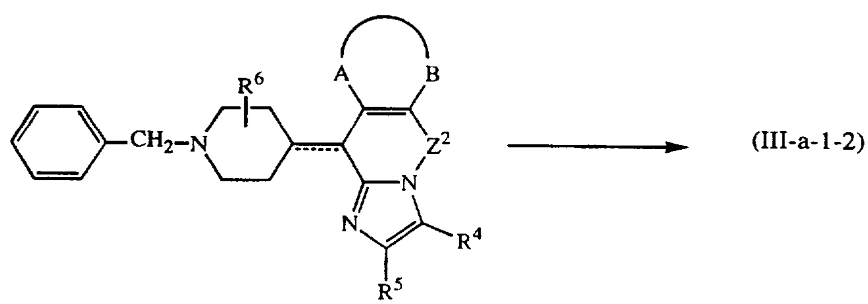
The compounds of formula (I) may also be converted into each other following art-known transformations. For instance, compounds of formula (I) wherein R^4, R^5 or both R^4 and R^5 are hydroxyC_{1-6}alkyl may be oxidized to the corresponding aldehyde or carboxylic acid by reaction with suitable reagents such as, for example, manganese(IV) oxide, respectively, silver nitrate.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid,

peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

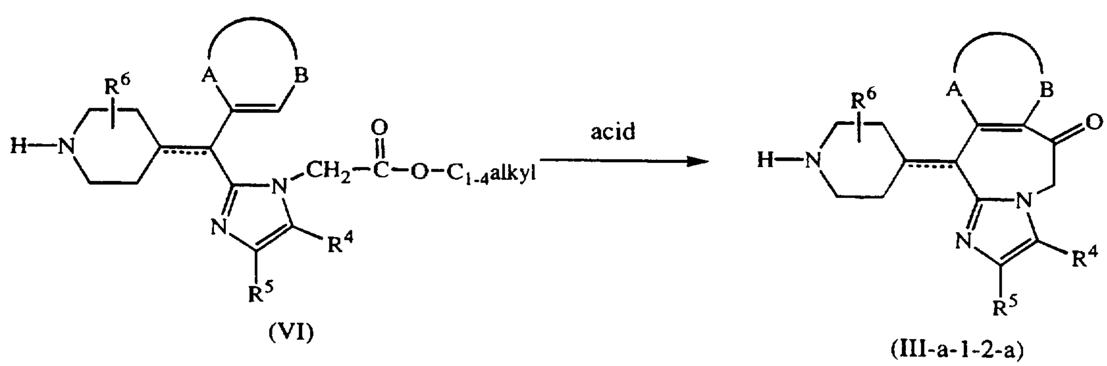
The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of formula (III) wherein L is a radical of formula (a-1) wherein Z is Z^1, said intermediates being represented by formula (III-a-1-1), may be prepared as described in EP-0,518,435-A, EP-0,518,434-A and EP-0,672,047-A.

The intermediates of formula (III) wherein L is a radical of formula (a-1) wherein Z is Z^2, said intermediates being represented by formula (III-a-1-2), may in general be prepared by debenzylating a compound of formula

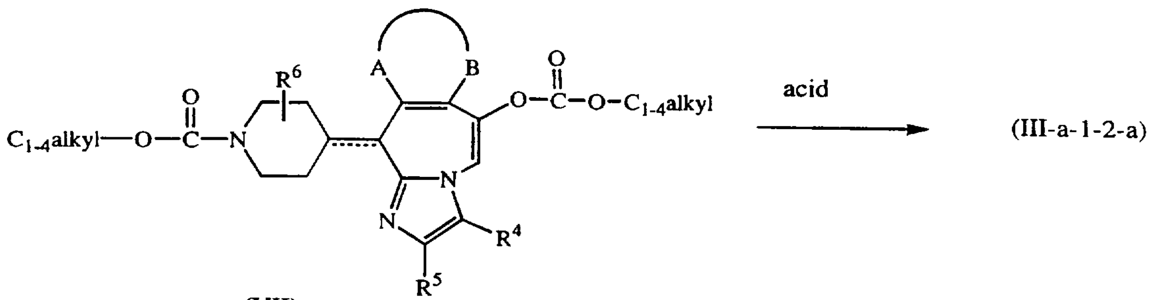


following art known procedures, e.g. catalytic hydrogenation.

In particular, the intermediates of formula (III-a-1-2) wherein Z^2 is a radical of formula -CH_2-C(=O)-, said intermediates being represented by formula (III-a-1-2-a), can be prepared by reacting an intermediate of formula (VI) in the presence of an acid, e.g. trifluoromethanesulfonic acid, and the like.

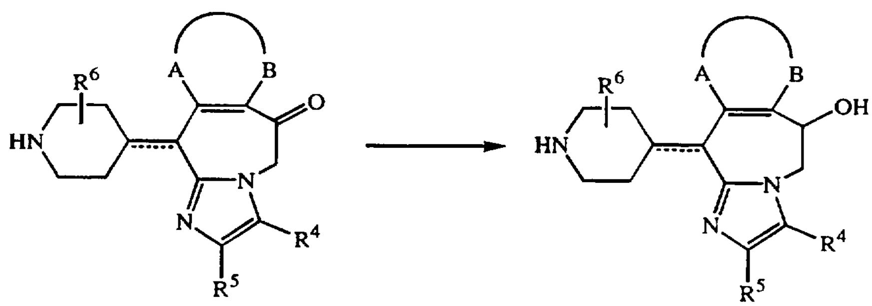


The intermediates of formula (III-a-1-2-a) can also be prepared by hydrolizing an intermediate of formula (VII) in the presence of an acid, e.g. hydrobromic acid, trifluoroacetic acid and the like.



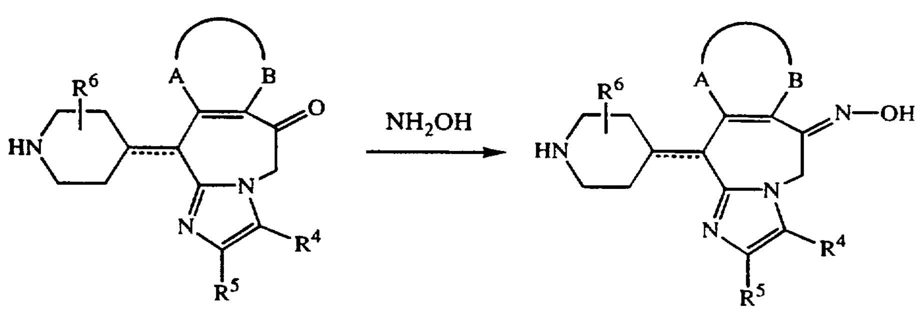
(VII)

The intermediates of formula (III-a-1-2) wherein Z^2 is a radical of formula $-CH_2-CHOH-$, said intermediates being represented by the formula (III-a-1-2-b), can be prepared by reacting the compounds of formula (III-a-1-2-a) in the presence of a reducing reagent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. methanol and the like.



(III-a-1-2-a) (III-a-1-2-b)

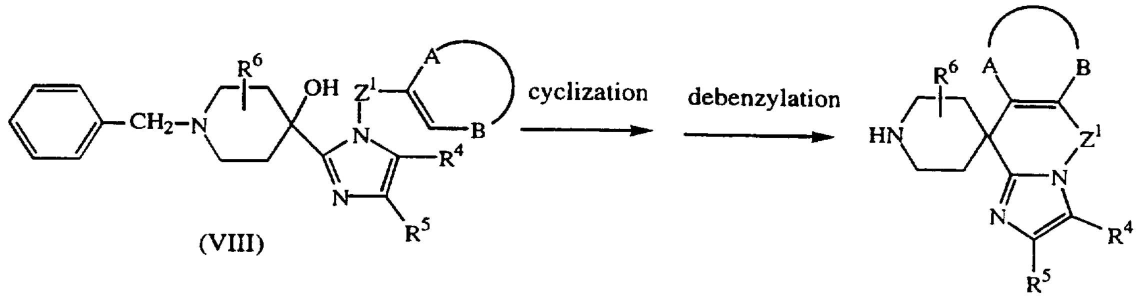
The intermediates of formula (III-a-1-2) wherein Z^2 is a radical of formula $-CH_2-C(=NOH)-$, said intermediates being represented by the formula (III-a-1-2-c), can be prepared by reacting the compounds of formula (III-a-1-2-a) with hydroxylamine or a salt, e.g. the hydrochloride salt thereof, in a reaction-inert solvent, e.g. pyridine and the like.



(III-a-1-2-a) (III-a-1-2-c)

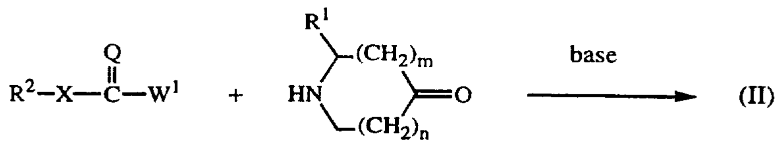
Intermediates of formula (III) wherein L is a radical of formula (a-2) wherein Z is Z^1, said intermediates being represented by formula (III-a-2-1), may be prepared by cyclizing an intermediate of formula (VIII) with a suitable reagent such as, for example, trifluoroacetic

acid, and subsequently, debenzylating the thus formed intermediate following art known procedures, e.g. catalytic hydrogenation.



(VIII) (III-a-2-1)

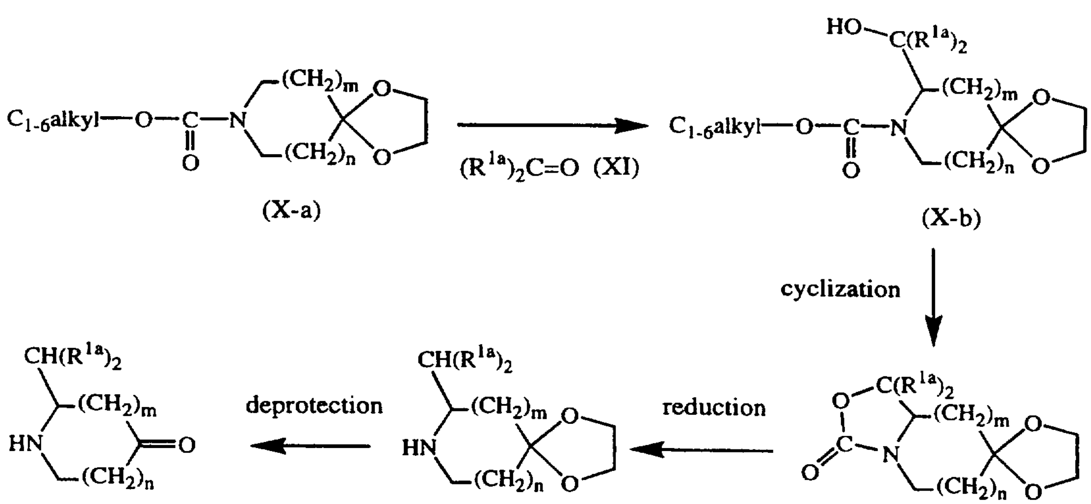
Intermediates of formula (II) may be prepared by condensing an intermediate of formula (IV) with an intermediate of formula (IX) analogous to the procedure described in EP-0,532,456-A.



(IV) (IX)

Ways to prepare intermediates of formula (IX) are also described in EP-0,532,456-A. However, intermediates of formula (IX) wherein R^1 is optionally substituted Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, said R^1 being represented by $-CH(R^{1a})_2$ and said intermediates being represented by formula (IX-a), may also be prepared as depicted in scheme 1.

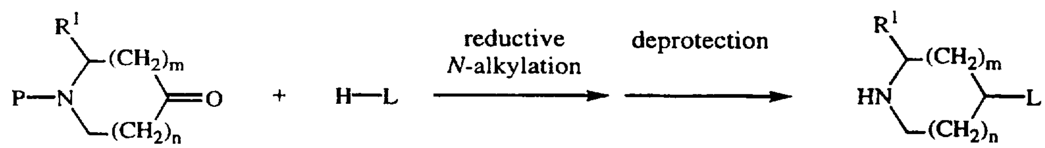
<u>Scheme 1</u>



(X-a) (X-b) (IX-a) (X-d) (X-c)

In scheme 1, the intermediates of formula (X-b) may be prepared by reacting an intermediate of formula (X-a) with an aldehyde or a ketone of formula (XI). The C_{1-6}alkylcarbamate moiety in the intermediates of formula (X-b) may be converted into a fused oxazolone which in turn may be reduced to an intermediate of formula (X-d). Said intermediate (X-d) may in turn be deprotected, thus forming an intermediate of formula (IX-a). Subsequently, intermediates of formula (IX-a) may be reacted with an intermediate of formula (IV) to prepare intermediates of formula (II) wherein R^1 is defined as $-CH(R^{1a})_2$, said intermediates being represented by formula (II-a). The reactions performed in scheme 1 may all be conducted following conventional methods that are generally known in the art.

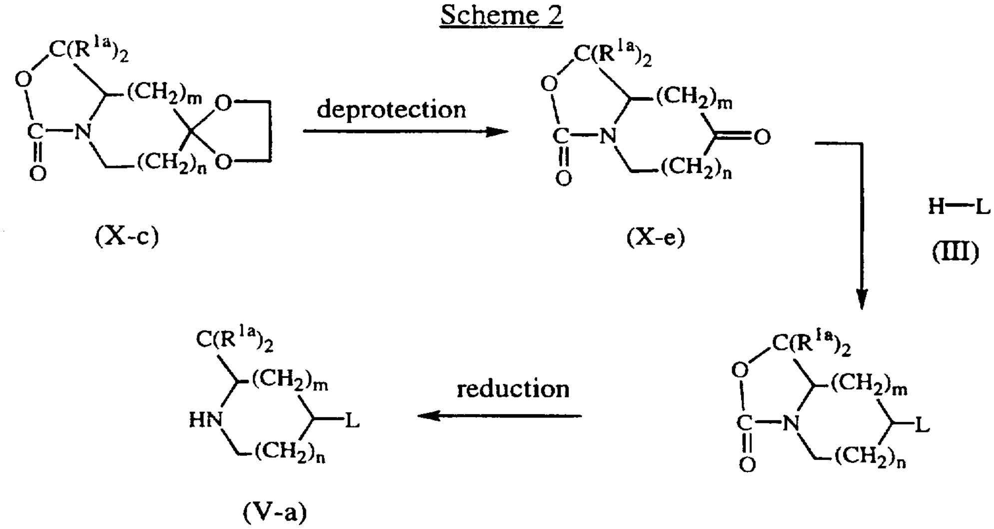
Intermediates of formula (V) may suitably be prepared by reacting an intermediate of formula (IX-1), being a protected intermediate of formula (IX) with a protecting group P such as, for example, a C_{1-6}alkyloxycarbonyl group, with an intermediate of formula (III) according to the previously described reductive *N*-alkylation procedure, and subsequently deprotecting the thus formed intermediate.



(IX-1) (III) (V)

In particular, intermediates of formula (V) wherein R^1 is $-CH(R^{1a})_2$, said intermediates being represented by formula (V-a), may be prepared as is depicted in scheme 2.

Scheme 2



The ketalized intermediate of formula (X-c) may be transformed to the corresponding ketone of formula (X-e) which subsequently may be reductively aminated with a

pyrrolidine, piperidine- or homopiperidine derivative of formula (III). The thus obtained intermediate may then be reduced with a suitable reducing agent to an intermediate of formula (V-a).

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) have valuable pharmacological properties in that they interact with tachykinin receptors and they antagonize tachykinin-induced effects, especially substance P-induced effects, both *in vivo* and *in vitro* and are thus of use in the treatment of tachykinin-mediated diseases, and in particular in substance P-mediated diseases.

Tachykinins, also referred to as neurokinins, are a family of peptides among which substance P (SP), neurokinin A (NKA), neurokinin B (NKB) and neuropeptide K (NPK) may be identified. They are naturally occurring in mammals, including human beings, and are distributed throughout the central and peripheral nervous system, where they act as neurotransmitters or neuromodulators. Their actions are mediated through several subtypes of receptors, such as, for example, NK_1, NK_2 and NK_3 receptors. Substance P displays highest affinity for NK_1 receptors, whereas NKA preferentially binds to NK_2 receptors and NKB preferentially binds to NK_3 receptors. However, the selectivity of these tachykinins is relatively poor and under physiological conditions the

action of any of these tachykinins might be mediated by activation of more than one receptor type.

Substance P and other neurokinins are involved in a variety of biological actions such as pain transmission (nociception), neurogenic inflammation, smooth muscle contraction, plasma protein extravasation, vasodilation, secretion, mast cell degranulation, and also in activation of the immune system. A number of diseases are deemed to be engendered by activation of neurokinin receptors, in particular the NK_1 receptor, by excessive release of substance P and other neurokinins in particular cells such as cells in the neuronal plexi of the gastrointestinal tract, unmyelinated primary sensory afferent neurons, sympathetic and parasympathetic neurons and nonneuronal cell types (DN&P 8(1), February 1995, p. 5-23, "Neurokinin Receptors" by Longmore J. et al.; Pharmacological Reviews 46(4), 1994, p. 551-599, "Receptors and Antagonists for Substance P and Related Peptides" by Regoli et al.).

The compounds of the present invention are potent inhibitors of neurokinin-mediated effects, in particular those mediated via the NK_1 receptor, and may therefore be described as tachykinin antagonists, especially as substance P antagonists, as indicated *in vitro* by the antagonism of substance P-induced relaxation of pig coronary arteries which is described hereinafter. The binding affinity of the present compounds for the human, guinea-pig and gerbil neurokinin receptors may be determined *in vitro* in a receptor binding test using ^{3}H-substance P as radioligand. The subject compounds also show substance-P antagonistic activity *in vivo* as may be evidenced by, for instance, the antagonism of substance P-induced plasma extravasation in guinea-pigs, or the antagonism of drug-induced emesis in ferrets (Watson et al., Br. J. Pharmacol. 115, 84-94, 1995).

In view of their capability to antagonize the actions of tachykinins by blocking the tachykinin receptors, and in particular antagonizing the actions of substance P by blocking the NK_1 receptor, the subject compounds are useful in the prophylactic and therapeutic treatment of tachykinin-mediated diseases such as, for example,

- pain, in particular traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS-related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain;

various forms of headache such as migraine, acute or chronic tension headache, temperomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain;

- respiratory and inflammatory diseases, in particular inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation;
- emesis, i.e. nausea, retching and vomiting, including acute emesis, delayed emesis and anticipatory emesis, no matter how emesis is induced, for example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5-fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia;
- central nervous system disorders, in particular psychoses such as schizophrenia, mania, dementia or other cognitive disorders e.g. Alzheimer's disease; anxiety; AIDS-related dementia; diabetic neuropathy; multiple sclerosis; depression; Parkinson's disease; and dependence on drugs or substances of abuse;

- allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis;
- gastrointestinal disorders, such as irritable bowel syndrome;
- skin disorders, such as psoriasis, pruritis and sunburn;
- vasospastic diseases, such as angina, vascular headache and Reynaud's disease;
- cerebral ischaemia, such as cerebral vasospasm following subarachnoid haemorrhage
- stroke, epilepsie, head trauma, spinal cord trauma and ischemic neuronal damage;
- fibrosing and collagen diseases, such as scleroderma and eosinophilic fascioliasis;
- disorders related to immune enhancement or suppression, such as systemic lupus erythematosus;
- rheumatic diseases, such as fibrositis;
- neoplastic disorders;
- cell proliferation; and
- cough.

The compounds of the present invention have a favourable metabolic stability and exhibit good oral availability. They also have an advantageous onset and duration of action. The compounds of formula (I) also have the ability to penetrate the central nervous system as may be demonstrated *in vivo* by their inhibitory effect on the change in behaviour induced by intracerebroventricular-applied substance P in the gerbil.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from tachykinin-mediated diseases as mentioned hereinabove, in particular, pain, emesis or asthma. Said method comprises the systemic administration of an effective tachykinin antagonizing amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans. Hence, the use of a compound of formula (I) as a medicine is provided, and in particular a medicine to treat pain, emesis or asthma.

For ease of administration, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable,

preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid or base addition salts of compounds of formula (I) due to their increased water solubility over the corresponding base or acid form, are obviously more suitable in the preparation of aqueous compositions.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α–, β– or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage

unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Those of skill in the treatment of tachykinin mediated diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.001 mg/kg to about 40 mg/kg body weight, more preferably from about 0.01 mg/kg to about 5 mg/kg body weight. It may be appropriate to administer the therapeutically effective dose once daily or as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.05 mg to 500 mg, and in particular, 0.5 mg to 50 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the patient may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated patient and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

The following examples are intended to illustrate and not to limit the scope of the present invention.

Experimental part

Hereinafter, "THF" means tetrahydrofuran, “RT” means room temperature. Of some compounds of formula (I) the absolute stereochemical configuration was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as “A” and the second as “B”, without further reference to the actual stereochemical configuration.

A. Preparation of the intermediate compounds

Example A1

a) A mixture of *N*-(1-methylethyl)-2-propanamine (16.7 g) in THF (600ml) was stirred at -70°C under N_2 flow. Butyllithium in hexane (63 ml; 2.5 M) was added portionwise and the temperature was allowed to rise to -40°C and stirring was continued for 15 minutes. The mixture was cooled to -70°C and a suspension of 1-(phenylmethyl)benzimidazole (31.3 g) in THF was added dropwise. After stirring for 1 hour at -70°C, 4-(ethoxy-carbonyl)-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (42.5 g) was added dropwise and stirring at -70°C was continued for 1.5 hours. The temperature was allowed to rise to RT and the mixture was decomposed with water, and further extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent evaporated. The residue was crystallized from acetonitrile, yielding 54 g (85.8%) of (1,1-dimethylethyl) 4-[[1-(phenylmethyl)-1*H*-benzimidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 1; mp. 121.5°C).

b) A mixture of intermediate (1) (25.2 g) and hydrochloric acid in 2-propanol (60 ml) in methanol (400 ml) was stirred and refluxed for 1 hour. The solvent was evaporated, crystallized from 2-propanol and recrystallized from ethanol, yielding 20.7 g (97%) of [1-(phenylmethyl)-1*H*-benzimidazol-2-yl](4-piperidinyl)methanone monohydrochloride (interm. 2; mp. 197.7°C).

c) Intermediate (2) (10.7 g) was dissolved in H_2O and alkalized with K_2CO_3. The free base was extracted with CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated. The residue was dissolved in methanol (100 ml), sodium borohydride (4 g) was added and the mixture was stirred during 1 hour at RT. The solvent was evaporated, then dissolved in H_2O/CH_2Cl_2 and extracted with CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated. The concentrate was boiled in CH_3CN, yielding 8.1 g (84%) of 1-(phenylmethyl)-α-(4-piperidinyl)-1*H*-benzimidazole-2-methanol (interm. 3);

d) Intermediate (3) (6.4 g) was stirred overnight in trifluoromethanesulfonic acid (25 ml) under N_2-flow. The reaction mixture was poured out into ice, alkalized with NaOH and extracted with CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent:CH_2Cl_2 / (CH_3OH/NH_3) 90/10). The pure fractions were collected and evaporated, yielding 5.4 g of 6,11-dihydro-6-(4-piperidinyl)benzimidazo[1,2-b]isoquinoline (interm. 4a). A sample (1.4 g) was converted into the cyclohexanesulfamic acid salt (1:2) in CH_3CN/C_2H_5OH, yielding 2.84 g of 6,11-dihydro-6-(4-piperidinyl)benzimidazo[1,2-b]isoquinoline cyclohexylsulfamate (1:2) (interm. 4; mp. 205.8°C).

Example A2

a) A mixture of *N*-(1-methylethyl)-2-propanamine (26.3 g) in THF (800ml) was stirred under N_2 and the mixture was cooled to -70°C. Butyllithium in hexane (104 ml; 2.5 M)

was added portionwise and the mixture was brought to -40°C and stirred for 15 minutes. 1-(2-phenylethyl)-1*H*-imidazole (34.4 g) dissolved in THF was added dropwise at -70°C and the mixture was stirred for 1 hour. 1-(Phenylmethyl)-4-piperidinone (45.4 g) dissolved in THF was added dropwise at -70°C and the mixture was stirred for 1 hour. The mixture was brought to RT and stirred at RT for 18 hours. The mixture was decomposed with water and the solvent evaporated. The residue was taken up in water, extracted with CH_2Cl_2, dried and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3). The pure fractions were collected and the solvent evaporated. A sample (1.5 g) was converted into the (Z)-2-butenedioic acid salt (1:2) in 2-propanone, yielding 1.92 g of 4-[1-(2-phenyl-ethyl)-1*H*-imidazol-2-yl]-1-(phenylmethyl)-4-piperidinol (Z)-2-butenedioate (1:2) (interm. 5; mp. 156.4°C).

b) A mixture of the free base of intermediate (5) (36 g) in trifluoroacetic acid (200 ml) was stirred at 70°C for 48 hours. The mixture was cooled, poured into ice water, alkalized with NaOH (50%), extracted with CH_2Cl_2, dried, filtered and the solvent evaporated. The residue was purified on a glass filter over silica gel (eluent : CH_2Cl_2/ CH_3OH 95/5). The pure fractions were collected and the solvent evaporated. The residue was converted into the (E)-2-butenedioic acid salt (1:2) in ethanol, yielding 38.7 g (67%) of 6,11-dihydro-1'-(phenylmethyl)-5*H*-spiro[imidazo[1,2-b][3]benzazepine-11,4'-piperidine] (E)-2-butene-dioate(1:2) (interm. 6; mp. 214.3°C).

c) A mixture of the free base of intermediate (6) (6.9 g) in methanol (150 ml) was hydrogenated with palladium on activated carbon (10%; 2 g) as a catalyst at 50 °C for 18 hours. After uptake of hydrogen, the catalyst was filtered and the filtrate was evaporated, yielding 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*], 4'-piperidine] (interm. 7a). A sample was converted into the hydrochloric acid salt (1:1) in CH_3CN, yielding 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*], 4'-piperidine] . monohydrochloride (interm. 7; mp. 278.5°C).

Example A3

a) A mixture of 1,1-dimethylethyl 1,4-dioxo-8-azaspiro[4.5]-8-carboxylate (0.1 mol) in diethylether (150ml) and N,N,N',N'-tetramethyl-ethylenediamine (33.2ml) was cooled on a 2-propanol/CO_2 bath under a N_2 flow. Sec. buthyllithium (1.3 M; 0.11 mol) was added dropwise at a temperature below -60°C and the mixture was stirred for 3 hours. A mixture of 3,5-(difluoro)benzaldehyde (0.12 mol) in diethylether (75ml) was added dropwise. The mixture was stirred slowly overnight and allowed to warm to RT. The mixture was decomposed with water and separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried, filtered and the

solvent was evaporated, yielding 38.5g of (±)-1,1-dimethylethyl 7-[(3,4-difluorophenyl)hydroxymethyl]-1,4-dioxa-8-azaspiro[4.5]-decane-8-carboxylate (interm. 8).
b) A mixture of intermediate 8 (0.1 mol) and 2-methyl-2-propanol, potassium salt (1g) in toluene (200ml) was stirred and refluxed for 2 hours. The solvent was evaporated and the residue was taken up in CH_2Cl_2/water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was suspended in petroleum ether and the precipitate was filtered off and dried, yielding 10g (32%) of (±)-1'-(3,4-difluorophenyl)-tetrahydrospiro[1,3-dioxolan-2,7'(1'H)-[3H]-oxazolo[3,4-a]pyridin]-3-one (interm. 9).
c) A mixture of intermediate 9 (0.032 mol) in methanol (250ml) was hydrogenated at 50°C with palladium on activated carbon (10%; 2g) as a catalyst. After uptake of hydrogen, the catalyst was filtered off and the filtrate was evaporated, yielding 9g (100%) of (±)-2-[(3,4-difluorophenyl)methyl]-1,4-dioxa-8-azaspiro[4.5]decane (interm. 10).
d) A mixture of intermediate 10 (0.032 mol) in HCl, (6N; 90ml) was stirred at 75°C, then cooled. CH_2Cl_2 was added and the mixture was alkalized with NaOH at a temperature below 20°C. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was dried, yielding 7.2g of (±)-2-[(3,4-difluorophenyl)methyl]-4-piperidinone (interm. 11).
In a similar way as described in procedure d), (±)-2-(phenylmethyl)-4-piperidinone (interm. 12) was prepared.
e) A mixture of intermediate 12 in CH_2Cl_2, 3,5-dimethylbenzoyl chloride (7.4 g) and triethylamine (11 ml) was stirred overnight at RT. Dilute NaOH was added. The organic layer was separated, dried, filtered and the solvent evaporated. The residue was crystallized from diisopropylether yielding 7.44 g (58%) of (±)-1-(3,5)-dimethylbenzoyl)-2-(phenylmethyl)-4-piperidinone (interm. 13).
In a similar way as described in procedure e), (±)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-difluorophenyl)methyl]-4-piperidinone (interm. 14) was prepared.

Example A4

A mixture of (±)-8-*tert*-butoxycarbonyl-7-(phenylmethyl)-1,4-dioxa-8-azaspiro[4.5]-decane (33.34 g) in HCl, 6 N (250 ml) was stirred at 70°C for 1 hour 30 minutes. The mixture was cooled, CH_2Cl_2 (100 ml) was added and the mixture was alkalized with NaOH while cooling till 25°C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Triethylamine (20.2 g), followed by 3,5-bis(trifluoromethyl)benzoyl chloride (27.7 g) dissolved in a little CH_2Cl_2 were added and the

mixture was stirred for 2 hours. Water was added and the layers were separated. The organic layer was dried, filtered and evaporated. The residue was crystallized from DIPE, the precipitate was filtered off and dried, yielding a first crop. The mother layer was evaporated and the residue was crystallized from diisopropylether. The precipitate was filtered off and dried, yielding a second crop. The two solid fractions were put together and taken up in water and CH_2Cl_2. NaOH was added and the mixture was extracted. The organic layer was dried, filtered off and evaporated, yielding 16.14 g (38%) (±)-1-[3,5-bis-(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinone (interm. 15, mp. 102.5 °C).

B. Preparation of the final compounds

Example B1

A mixture of (±)-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)-4-piperidinone (2.5 g) and 6,11-dihydro-11-(4-piperidinylidene)-5*H*-imidazo[2,1-b][3]benzazepine (2.1 g) in methanol (150 ml) and a solution of thiophene (4%; 1 ml) was hydrogenated at 50°C overnight with palladium on activated carbon (10%; 2 g) as a catalyst. After uptake of hydrogen, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/ (CH_3OH/ NH_3) 98/2 to 95/5). The desired fraction was collected, the solvent evaporated, yielding 0.54 g (12.3%) of (±)-*cis*-4-[4-(5,6-dihydro-11*H*-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine (comp. 1; mp. 138.7°C).

Example B2

a) The free base of intermediate (4) (3 g) was added to (±)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(phenylmethyl)-4-piperidinone (4.3 g) in CH_2Cl_2 (40 ml). Titanium(IV)-isopropoxide (3.41 g) was added and the mixture was stirred for 3 hours at RT. Ethanol (15 ml) and sodium cyanoborohydride (0.62 g) were added and the resulting reaction mixture was stirred overnight at RT. Water (5 ml) was added and the mixture was filtered over dicalite and the filtrate was evaporated. The residue was partitioned between water and CH_2Cl_2. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The separated organic layer was dried, filtered, and the solvent was evaporated. The residue was purified by HPLC (eluent: (0.5% ammoniumacetate in H_2O)/CH_3OH 30/70), yielding two desired fractions. A first fraction yielded 0.63 g (9%) (±)-*cis*-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(6,11-dihydrobenzimidazo[1,2-b]isoquinolin-6-yl)-1-piperidinyl]-2-phenylmethyl)piperidine. (comp. 14; mp. 132.2°C). A second fraction yielded 0.32 g (5%) of (±)-*trans*-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(6,11-dihydro-benzimidazo[1,2-b]isoquinolin-6-yl)-1-piperidinyl]-2-phenylmethyl)piperidine (comp. 15; mp. 138.1°C).

b) A mixture of intermediate 8 (0.02 mol) and 5,6-dihydrospiro[11H-imidazo[2,1-b]-[3]benzazepine-11,4'-piperidine] (0.02 mol) in 2-propanol (20ml) was stirred at RT. Titanium(IV)isopropoxide (0.024 mol) was added. The mixture was stirred at 40°C for 3 hours and then cooled to RT. Ethanol (140ml) and sodiumborohydride (0.2 mol) were added. The mixture was stirred at RT overnight. Water was added, the mixture was filtered over celite and the filtrate was evaporated. The residue was taken up in water and CH_2Cl_2, and the mixture was separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2 to 95/5). Two pure fractions were collected and their solvents were evaporated, yielding 1.41g (13%) of (±)-cis-4-(5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-1-yl)-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine (comp. 119) and 2.36g (21%) of (±)-trans-4-(5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-1-yl)-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine (comp. 120).

Example B3

Sodium triacetoxyborohydride (8.5 g) and acetic acid (2.4 g) were added dropwise to a mixture of (±)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinone (4.3 g) and 5,6,7,10-tetrahydro-7-methyl-10-(4-piperidinylidene)imidazo[1,2-a]pyrrolo-[3,2-d]azepine (2.7 g) in 1,2-dichloroethane (100ml) and the mixture was stirred at RT overnight. Water and K_2CO_3 (5 g) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, filtered and the solvent evaporated. The residue was purified by HPLC over silica gel (eluent : CH_2Cl_2/CH_3OH 96/4 to 85/15). The pure fractions were collected and evaporated, yielding 1.04 g (15%) of fraction 1 and 0.26 g (4%) of (±)-*trans*-1-[3,5-bis-(trifluoromethyl)benzoyl]-4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine (comp. 2; mp. 141.5°C). Fraction 1 was repurified by HPLC over NH_2-Kromasil (eluent: 100% CH_2Cl_2). The pure fractions were collected and the solvent was evaporated, yielding 0.75 g (11%) of (±)-*cis*-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]-pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine (comp. 3; mp. 133.0°C).

Example B4

A mixture of (±)-*cis*-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[5,6-dihydro-3-(hydroxy-methyl)-11*H*-imidazo[2,1-b][3]benzazepin-11-ylidene]-1-piperidinyl]-2-(phenylmethyl)-piperidine (4.5 g) and manganese dioxide (20 g) in $CHCl_3$ (200 ml) was stirred and refluxed for 1 hour. The mixture was filtered warm over dicalite and the filtrate was

evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was purified by HPLC (eluent: CH_2Cl_2/CH_3OH 100/0 to 95/5). The pure fractions were collected and the solvent was evaporated, yielding 3.1 g (70%) of (±)-*cis*-1-[3,5-bis-(trifluoromethyl)benzoyl]-4-[4-(3-formyl-5,6-dihydro-11*H*-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine (comp. 11; mp. 125.8°C).

Example B5

A mixture of compound 11 (0.00345 mol), sodium cyanide (0.0189 mol) and manganese dioxide (0.069 mol) in methanol (50ml) was stirred at RT. Acetic acid (1.2ml) was added dropwise. The mixture was stirred and refluxed overnight, then cooled and filtered over dicalite. The filtrate was evaporated. The residue was taken up in water/CH_2Cl_2. K_2CO_3 (2g) was added and the mixture was separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3;). The pure fractions were collected and the solvent was evaporated, yielding 2g (79%).of (±)-methyl cis-11-[1-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-4-piperidinylidene]-6,11-dihydro-5*H*-imidazo[2,1-b][3]benzazepine-3-carboxylate (comp. 17).

Example B6

3,5-di(trifluoromethyl)benzoyl chloride (0.003 mol) and then triethylamine (0.0045 mol) were added dropwise to a mixture of (±)-trans-6-[1-[2-[(3,4-dichloro-phenyl)-methyl]-4-piperidinyl]-4-piperidinyl]-11,12-dihydro-6H-benzimidazo[2,1-b]-[3]benzazepine (0.003 mol) in CH_2Cl_2 (25ml). The mixture was stirred at RT overnight, washed with water and separated into its layers. The organic layer was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 98/2 to 96/4). The pure fractions were collected and the solvent was evaporated. The residue was dried, yielding 1.23g (51%) of (±)-trans-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-dichlorophenyl)methyl]-4-[4-(11,12-dihydro-6H-benzimidazo[2,1-b][3]benzazepin-6-yl)-1-piperidinyl]piperidine (comp. 63).

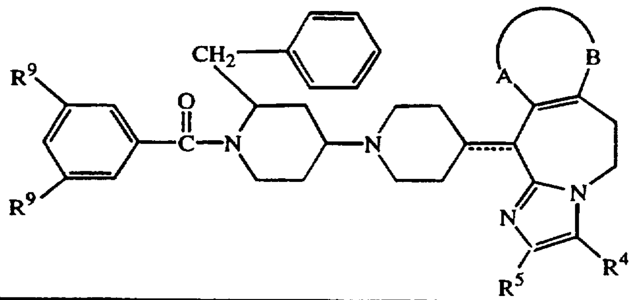
Example B7

(±)-trans-6,11-dihydro-11-[1-[2-(phenylmethyl)-4-piperidinyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b][3]benzazepine (0.00023 mol) was added to 1*H*-indole-5-carboxylic acid (± 0.080 g) and 1*H*-benzotriazole-1-ol (0.060 g) in CH_2Cl_2 (3 ml). The mixture was

stirred and cooled on an ice-bath, under N_2 flow. Triethylamine (0.5 ml) was added dropwise. A solution of $(CH_3)_2$-N-$(CH_2)_3$-N=N-CH_2-CH_3 (0.080 g) in CH_2Cl_2 (5 ml) was added dropwise and the reaction mixture was allowed to warm to RT, under N_2. The reaction mixture was stirred overnight. The solvent was evaporated and the residue was purified by HPLC (eluent gradient: (0.5% ammoniumacetate in H_2O)/CH_3OH/CH_3CN 70/15/15 upgrading over 0/50/50 to 0/0/100). The desired fractions were collected and the solvent was evaporated, yielding 0.040 g of (±)-*trans*-*N*-(2,6-dimethylphenyl)-4-[2-(phenylmethyl)-4-piperidinyl]-1-piperazineacetamide (comp. 81).

The following tables list compounds of formula (I) as prepared according to one of the above examples (Ex. No.).

Table 1



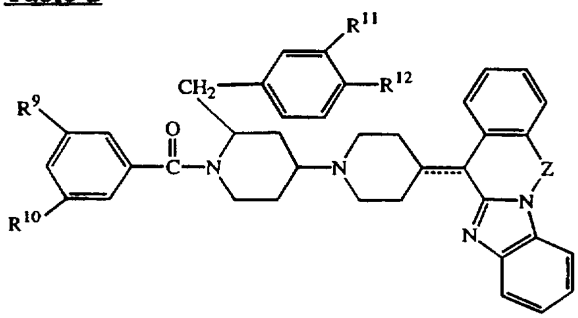
Co. No	Ex. No	R^9	R^4	R^5	-A-B-	------ &	physical data (mp in °C)
1	B1	CH_3	H	H	-CH=CH-CH=CH-	d.b.	mp. 138.7; (±)-*cis*
2	B3	CF_3	H	H	-CH=CH-N(CH_3)-	d.b.	mp. 141.5; (±)-*trans*
3	B3	CF_3	H	H	-CH=CH-N(CH_3)-	d.b.	mp. 133.0; (±)-*cis*
4	B2a	CF_3	CH_2OH	H	-CH=CH-CH=CH-	d.b.	mp. 156.2; (±)-*cis*
5	B2a	CF_3	CH_2OH	H	-CH=CH-CH=CH-	d.b.	mp. 135.9; (±)-*trans*
6	B2a	CF_3	H	H	-S-CH=CH-	d.b.	mp. 128.5; (±)-*cis*
7	B2a	CF_3	H	H	-S-CH=CH-	d.b.	mp. 128.6; (±)-*trans*
8	B2a	CF_3	H	H	-CH=CH-CH=CH-	s.b.	mp. 114.7; (±)-*trans*
9	B2a	CF_3	H	H	-CH=CH-CH=CH-	s.b.	mp. 114.5; (A)-*cis*
10	B2a	CF_3	H	H	-CH=CH-CH=CH-	s.b.	mp. 112.5; (B)-*cis*
11	B4	CF_3	C(=O)H	H	-CH=CH-CH=CH-	d.b.	mp. 125.8; (±)-*cis*
16	B4	CF_3	C(=O)H	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
17	B5	CF_3	C(=O)OH	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
18	B2	CF_3	H	H	-CH=CH-S-	d.b.	(±)-*cis*
19	B2	CF_3	H	H	-CH=CH-S-	d.b.	(±)-*trans*
20	B2b	CH_3	CH_2OH	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*

Co. No	Ex. No	R^9	R^4	R^5	-A-B-	$\overline{\cdots\cdots}$ &	physical data (mp in °C)
21	B2b	CH_3	CH_2OH	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
22	B2b	CF_3	H	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
23	B2b	CF_3	H	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
24	B4	CH_3	C(=O)H	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
25	B4	CH_3	C(=O)H	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
26	B2b	CH_3	H	H	-CH=CH-CH=CH-	s.b.	(±)-*cis*
27	B2b	CH_3	H	H	-CH=CH-CH=CH-	s.b.	(±)-*trans*
28	B2b	CH_3	CH_3	H	-CH=CH-CH=CH-	d.b.	(±)-(*cis* + *trans*)
29	B2b	CH_3	H	H	-CH=CH-CH=C(CH_3)-	d.b.	(±)-(*cis* + *trans*)
30	B2b	CH_3	H	CH_3	-CH=CH-N(CH_3)-	d.b.	(±)-(*cis* + *trans*)
31	B2b	CH_3	H	H	-CH=CH-C(Cl)=CH-	d.b.	(±)-(*cis* + *trans*)
32	B2b	CF_3	H	H	-CH=CH-C(Cl)=CH-	d.b.	(±)-(*cis* + *trans*)
33	B2b	CH_3	H	H	-CH=CH-N(CH_3)-	d.b.	(±)-*cis*
34	B2b	CH_3	H	H	-CH=CH-N(CH_3)-	d.b.	(±)-*trans*
35	B2b	CH_3	H	H	-S-CH=CH-	d.b.	(±)-*cis*
36	B2b	CH_3	—C(=O)—OCH_3	H	-S-CH=CH-	d.b.	(±)-*trans*
37	B2b	CH_3	H	H	-S-CH=CH-	d.b.	(±)-*trans*
38	B2b	CH_3	H	H	-CH=CH-S-	d.b.	(±)-*cis*
39	B2b	CH_3	H	H	-CH=CH-S-	d.b.	(±)-*trans*
40	B5	CH_3	—C(=O)—OCH_3	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
41	B6	CH_3	H	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
42	B2b	CH_3	CH_2OH	CH_2OH	-CH=CH-CH=CH-	d.b.	(±)-*trans*
43	B2b	CH_3	Cl	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
44	B2b	CH_3	Cl	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
47	B6	H	H	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
48	B6	Cl	H	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
49	B2b	CF_3	CH_2OH	CH_2OH	-CH=CH-CH=CH-	d.b.	(±)-*trans*
50	B2b	CF_3	H	H	-CH=CH-C(CH_3)=CH-	d.b.	(±)-*cis*
51	B2b	CF_3	H	H	-CH=CH-C(CH_3)=CH-	d.b.	(±)-*trans*
52	B2b	CF_3	CH_2OH	CH_2OH	-CH=CH-CH=CH-	d.b.	(±)-*cis*
53	B2b	CF_3	CH_3	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
54	B2b	CF_3	CH_3	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
55	B6	H	H	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*
56	B2b	CH_3	H	H	-CH=CH-C(CH_3)=CH-	d.b.	(±)-*cis*
57	B2b	CH_3	H	H	-CH=CH-C(CH_3)=CH-	d.b.	(±)-*trans*

Co. No	Ex. No	R^9	R^4	R^5	-A-B-	┈┈ &	physical data (mp in °C)
58	B2b	CF_3	Cl	H	-CH=CH-CH=CH-	d.b.	(±)-*trans*
59	B2b	CF_3	H	CH_3	-CH=CH-N(CH_3)-	d.b.	(±)-*cis*
60	B2b	CF_3	H	CH_3	-CH=CH-N(CH_3)-	d.b.	(±)-*trans*
61	B2b	CH_3	CH_2OH	CH_2OH	-CH=CH-CH=CH-	d.b.	(±)-*cis*
62	B2b	CF_3	Cl	H	-CH=CH-CH=CH-	d.b.	(±)-*cis*

& d.b. means double bond and s.b. means single bond

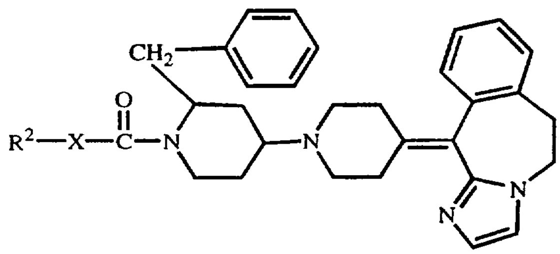
Table 2



Co. No.	Ex. No.	R^9	R^{10}	R^{11}	R^{12}	┈┈ &	-Z-	physical data
12	B2a	CF_3	CF_3	H	H	s.b.	-CH_2-CH_2-	mp 153.9; (±)-*cis*
13	B2a	CF_3	CF_3	H	H	s.b.	-CH_2-CH_2-	mp 173.5; (±)-*trans*
14	B2a	CF_3	CF_3	H	H	s.b.	-CH_2-	mp 132.2; (±)-*cis*
15	B2a	CF_3	CF_3	H	H	s.b.	-CH_2-	mp 138.1; (±)-*trans*
45	B2b	CH_3	CH_3	H	H	d.b	-CH_2-CH_2-	(±)-*cis*
46	B2b	CH_3	CH_3	H	H	d.b.	-CH_2-CH_2-	(±)-*trans*
63	B6	CF_3	CF_3	Cl	Cl	s.b.	-CH_2-CH_2-	(±)-*trans*
64	B6	CF_3	CF_3	Cl	Cl	s.b.	-CH_2-CH_2-	(±)-*cis*
65	B2b	CH_3	CH_3	H	H	s.b.	-CH_2-CH_2-	(±)-*cis*
66	B2b	CH_3	CH_3	H	H	s.b.	-CH_2-CH_2-	(±)-*trans*
67	B2b	CF_3	CF_3	F	F	s.b.	-CH_2-CH_2-	(±)-*cis*
68	B2b	CF_3	CF_3	F	F	s.b.	-CH_2-CH_2-	(±)-*trans*
69	B2b	CH_3	CH_3	H	H	s.b.	-CH_2-	(±)-*cis*
70	B2b	CH_3	CH_3	H	H	s.b.	-CH_2-	(±)-*trans*
71	B2b	CF_3	CF_3	H	H	d.b.	-CH_2-CH_2-	(±)-*cis*
72	B2b	CF_3	CF_3	H	H	d.b.	-CH_2-CH_2-	(±)-*trans*
73	B6	H	H	H	H	s.b.	-CH_2-	(±)-*cis*
74	B6	H	CF_3	H	H	s.b.	-CH_2-	(±)-*cis*
75	B6	H	H	H	H	s.b.	-CH_2-	(±)-*trans*

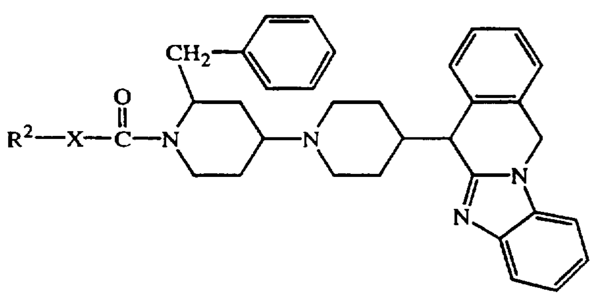
& d.b. means double bond and s.b. means single bond

Table 3



Co.No	Ex.No	R^2	X	physical data
76	B6	4-(methoxycarbonyl)phenyl	direct bond	(±)-*trans*
77	B6	2-furanyl	direct bond	(±)-*trans*
78	B6	2-naphthalenyl	direct bond	(±)-*trans*
79	B6	2-quinolinyl	direct bond	(±)-*trans*
80	B6	3,5-di(trifluoromethyl)phenyl	NH	(±)-*trans*
81	B7	1*H*-indol-5-yl	direct bond	(±)-*trans*
82	B6	2,3,4-trimethoxyphenyl	direct bond	(±)-*cis*
83	B6	2-thienyl	direct bond	(±)-*cis*
84	B6	2-naphthalenyl	direct bond	(±)-*cis*
85	B6	1-phenylethyl	direct bond	(±)-*cis*
86	B6	benzyl	O	(±)-*cis*
87	B7	5-methyl-2-pyrazinyl	direct bond	(±)-*cis*
88	B7	3-methylbenzofuran-2-yl	direct bond	(±)-*cis*
89	B7	5-fluoro-1H-indol-2-yl	direct bond	(±)-*cis*

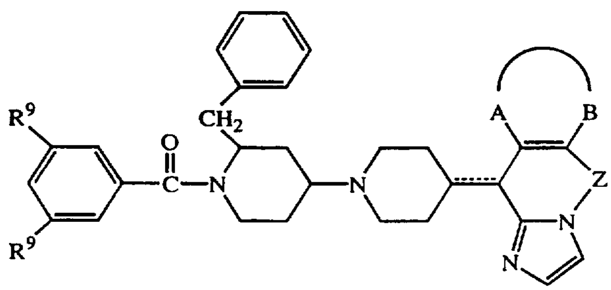
Table 4



Co.No	Ex.No	R^2	X	physical data
90	B6	2,4-dichlorophenyl	direct bond	(±)-*cis*
91	B6	2-thienyl	direct bond	(±)-*cis*
92	B6	2-naphthalenyl	direct bond	(±)-*cis*
93	B6	2-quinoxalinyl	direct bond	(±)-*cis*

Co.No	Ex.No	R^2	X	physical data
94	B6	2-benzothienyl	direct bond	(±)-*cis*
95	B6	1-phenylethyl	direct bond	(±)-*cis*
96	B7	6-benzothiazolyl	direct bond	(±)-*cis*
97	B6	5-methyl-3-isoxazolyl	direct bond	(±)-*trans*
98	B6	2-naphthalenyl	direct bond	(±)-*trans*
99	B6	1-phenylethyl	direct bond	(±)-*trans*
100	B6	3,5-di(trifluoromethyl)phenyl	NH	(±)-*trans*
101	B7	3-methylbenzofuran-2-yl	direct bond	(±)-*trans*
102	B7	6-benzothiazolyl	direct bond	(±)-*trans*
103	B7	3,4-dichlorophenyl	direct bond	(±)-*trans*

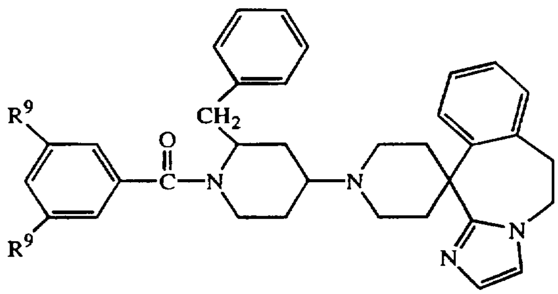
Table 5



Co.No	Ex. No	R^9	-Z-*	-A-B-	┉ &	physical data
104	B2b	CH_3	CH_2-O	-CH=CH-CH=CH-	d.b.	(±)-(*cis* + *trans*)
105	B2b	CF_3	CH_2-CH(OH)-	-CH=CH-S-	d.b.	(±)-A
106	B4	CF_3	CH_2-C(=O)-	-CH=CH-S-	d.b.	(±)-*cis*
107	B4	CF_3	CH_2-C(=O)-	-CH=CH-S-	d.b.	(±)-*trans*
108	B2b	CH_3	CH_2	-CH=CH-CH=CH-	s.b.	(±)-*cis*
109	B2b	CH_3	CH_2	-CH=CH-CH=CH-	s.b.	(±)-*trans*
110	B2b	CH_3	CH_2-CH(OH)-	-CH=CH-S-	d.b.	(±)-B
111	B4	CH_3	CH_2-C(=O)-	-CH=CH-S-	d.b.	(±)-*cis*
112	B4	CH_3	CH_2-C(=O)-	-CH=CH-S-	d.b.	(±)-*trans*
113	B2b	CF_3	CH_2-O	-CH=CH-CH=CH-	d.b.	(±)-*cis*
114	B2b	CF_3	CH_2-O	-CH=CH-CH=CH-	d.b.	(±)-*trans*
115	B2b	CF_3	CH_2	-CH=CH-CH=CH-	s.b.	(±)-*cis*
116	B2b	CF_3	CH_2	-CH=CH-CH=CH-	s.b.	(±)-*trans*

* the $-CH_2-$ group is always connected to the nitrogen of the imidazole moiety
& d.b. means double bond and s.b. means single bond

Table 6



Co.No	Ex. No	R^9	physical data
117	B2a	CF_3	(±)-*cis*
118	B2a	CF_3	(±)-*trans*
119	B2b	CH_3	(±)-*cis*
120	B2b	CH_3	(±)-*trans*

C. Pharmacological examples

Example C.1 : Antagonism of substance P induced relaxation of the pig coronary arteries

Segments of coronary arteries taken from pigs (killed by injection of an overdose of sodium pentobarbital) were inverted and mounted for recording of isometric tension in organ baths (volume 20 ml) with the endothelium at the outside. The preparations were bathed in Krebs - Henseleit solution. The solution was kept at 37 °C and gassed with a mixture of O_2 / CO_2 (95/5). After stabilisation of the preparations, prostaglandin $F_{2\alpha}$ (10^{-5} M) was administered to induce a contraction. This was repeated until contractile responses became stable. Then prostaglandin $F_{2\alpha}$ was again administered and substance P (3×10^{-10} M and 10^{-9} M cumulatively) was added. Substance P induced endothelium dependent relaxations. After washing away the agonists, a known concentration of a compound of formula (I) was added. After an incubation period of 30 minutes, prostaglandin $F_{2\alpha}$ (10^{-5} M) and the same concentrations of substance P as described above were again administered in the presence of the compound to be tested. Relaxations caused by substance P were expressed as relaxations under control conditions, and percentage inhibition (% inhibition) of the response to 10^{-9} M substance-P was taken as a measure of the antagonistic activity of the compound to be tested. The results for the compounds of the present invention at a certain test concentration are listed in table 7.

Table 7

Comp. No.	Concentration test compound	% inhibition
1	3×10^{-8}	52.3
2	3×10^{-8}	96.5
3	3×10^{-9}	37.3
4	3×10^{-8}	97.0
5	3×10^{-9}	100.0
6	3×10^{-8}	93.9
7	3×10^{-9}	83.1
8	3×10^{-9}	82.3
9	3×10^{-8}	100.0
10	3×10^{-8}	17.9
11	3×10^{-9}	96.1
12	3×10^{-8}	93.2
13	3×10^{-9}	74.2
14	3×10^{-9}	56.6
15	3×10^{-8}	95.4
16	3×10^{-9}	98.9
17	3×10^{-9}	35.3
18	3×10^{-9}	39.8
19	3×10^{-9}	78.1
20	3×10^{-9}	9.5
22	3×10^{-9}	83.2
23	3×10^{-9}	13.4
24	3×10^{-9}	38.3
25	3×10^{-9}	100.0
26	3×10^{-9}	25.6
27	3×10^{-9}	5.1
28	3×10^{-9}	37.4
29	3×10^{-9}	8.1
30	3×10^{-9}	15.3
31	3×10^{-9}	82.7
32	3×10^{-9}	71.6
34	3×10^{-9}	43.5
35	3×10^{-9}	27.7
36	3×10^{-9}	23.7
57	3×10^{-9}	66.7
58	3×10^{-9}	91.5
59	3×10^{-9}	76.5
60	3×10^{-9}	89.9
61	3×10^{-9}	7.5
62	3×10^{-9}	49.0
63	3×10^{-9}	61.4
64	3×10^{-9}	26.4
65	3×10^{-9}	27.3
66	3×10^{-9}	56.6
67	3×10^{-9}	64.4
68	3×10^{-9}	93.1
69	3×10^{-9}	8
70	3×10^{-9}	31.2
71	3×10^{-9}	53.1
72	3×10^{-9}	97.4
73	3×10^{-9}	2.8
74	3×10^{-9}	8.6
75	3×10^{-9}	13.7
77	3×10^{-9}	3.2
78	3×10^{-9}	7.5
80	3×10^{-9}	10.9
81	3×10^{-9}	2.2
84	3×10^{-9}	2.4
85	3×10^{-9}	1.8
89	3×10^{-9}	1.1
91	3×10^{-9}	9.2
92	3×10^{-9}	6.7
93	3×10^{-9}	3.1
94	3×10^{-9}	8.2
96	3×10^{-9}	17.3
97	3×10^{-9}	5.8
98	3×10^{-9}	23.2
99	3×10^{-9}	18.2

Comp. No.	Concentration test compound	% inhibition
37	3×10^{-9}	81.9
38	3×10^{-9}	27.1
39	3×10^{-9}	42.9
40	3×10^{-9}	8.4
41	3×10^{-9}	40.6
43	3×10^{-9}	16
44	3×10^{-9}	63.9
45	3×10^{-9}	7.9
46	3×10^{-9}	54.3
48	3×10^{-9}	59.7
49	3×10^{-9}	52.5
50	3×10^{-9}	25
51	3×10^{-9}	86.3
52	3×10^{-9}	77.8
53	3×10^{-9}	44.4
54	3×10^{-9}	69.8
56	3×10^{-9}	9.5

Comp. No.	Concentration test compound	% inhibition
100	3×10^{-9}	13.9
101	3×10^{-9}	11.8
102	3×10^{-9}	17
103	3×10^{-9}	8.3
104	3×10^{-9}	83.0
106	3×10^{-9}	92.3
107	3×10^{-9}	96.3
108	3×10^{-9}	2.6
109	3×10^{-9}	13.5
111	3×10^{-9}	22.6
112	3×10^{-9}	66.7
113	3×10^{-9}	87.9
114	3×10^{-9}	100.0
115	3×10^{-9}	60.2
116	3×10^{-9}	69.6
119	3×10^{-9}	9.3
120	3×10^{-9}	7.7

Example C.2 : Antagonism of substance P induced plasma extravasation in guinea-pigs

Plasma extravasation was induced by injection of substance P (2 mg/kg) in the femoral artery of female guinea-pigs. Evans Blue dye (30 mg/kg) was injected simultaneously. The test compound or solvent was administered subcutaneous (s.c.) or orally (p.o.) 1 hour prior to substance P injection. 10 minutes after challenge, the animals were checked for blue colouring (a direct measure for plasma extravasation) of the nose, the forepaws, and the conjunctiva. 30 minutes after challenge, the animals were sacrificed by CO_2 gas inhalation and checked for blue colouring of the trachea and the urinary bladder. Doses which actively inhibit substance P-induced plasma extravasation are defined as thoses doses at which only 1/3 or less of the total surface area of the nose, forepaws, conjunctiva, trachea or urinary bladder are coloured blue by an intensive extravasation. Table 8 lists the lowest active doses (LAD) in mg/kg for the tested compounds.

Table 8

Co.No.	LAD (in mg/kg)					
	nose	forepaws	conjunctiva	trachea	urinary bladder	administration
1	10	10	10	10	10	s.c.
2	0.16	0.16	0.16	2.5	2.5	s.c.
3	2.5	2.5	2.5	10	10	s.c.
4	10	10	10	10	10	s.c.
5	2.5	2.5	2.5	10	10	p.o.
7	2.5	10	2.5	10	10	s.c.
8	2.5	2.5	10	10	10	s.c.
10	10	10	10	10	10	s.c.
11	10	10	10	10	10	p.o.
14	10	10	10	10	10	p.o.
15	10	10	10	10	10	p.o.
16	2.5	2.5	2.5	10	10	s.c.
17	10	10	10	10	10	p.o.
18	10	10	2.5	10	10	s.c.
19	2.5	2.5	2.5	2.5	10	s.c.
20	2.5	2.5	2.5	2.5	2.5	s.c.
22	10	10	10	10	10	s.c.
25	2.5	2.5	2.5	10	10	s.c.
26	10	10	10	10	10	s.c.
27	2.5	2.5	2.5	10	2.5	s.c.
34	0.63	0.63	2.5	0.63	0.63	s.c.
35	10	10	10	10	10	s.c.
37	2.5	2.5	2.5	10	10	s.c.
39	2.5	2.5	2.5	10	10	s.c.
41	10	10	2.5	10	10	s.c.
52	2.5	2.5	2.5	10	2.5	s.c.
53	10	10	10	10	10	s.c.
54	2.5	2.5	2.5	2.5	2.5	s.c.
72	10	10	10	10	10	p.o.
106	10	10	10	10	10	p.o.
107	10	10	10	10	10	p.o.

Co.No.	LAD (in mg/kg)					
	nose	forepaws	conjunctiva	trachea	urinary bladder	administration
108	10	10	10	10	10	s.c.
111	10	10	10	10	10	s.c.
112	0.63	0.63	0.63	10	2.5	s.c.
113	10	10	10	10	10	s.c.
114	2.5	10	2.5	10	10	s.c.
117	2.5	2.5	2.5	40	10	s.c.
118	10	10	10	10	10	s.c.
120	2.5	2.5	2.5	10	10	s.c.

D. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) a pharmaceutically acceptable addition salt, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

Example D.1 : ORAL SOLUTION

Methyl 4-hydroxybenzoate (9 g) and propyl 4-hydroxybenzoate (1 g) were dissolved in boiling purified water (4 l). In 3 l of this solution were dissolved first 2,3-dihydroxy-butanedioic acid (10 g) and thereafter A.I (20 g). The latter solution was combined with the remaining part of the former solution and 1,2,3-propanetriol (12 l) and sorbitol 70% solution (3 l) were added thereto. Sodium saccharin (40 g) were dissolved in water (500 ml) and raspberry (2 ml) and gooseberry essence (2 ml) were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example D.2 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinylpyrrolidone (10 g) in water (200 ml). The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

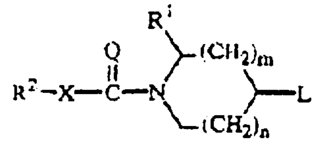
To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH_2Cl_2 (150 ml). Then there were added CH_2Cl_2 (75 ml) and 1,2,3-propanetriol (25 ml). Polyethylene glycol (10 g) was molten and dissolved in CH_2Cl_2 (75 ml). The latter solution was added to the former and then there were added agnesium octadecanoate (2.5 g), polyvinylpyrrolidone (5 g) and concentrated colour suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example D.3 : INJECTABLE SOLUTION

Methyl 4-hydroxybenzoate (1.8 g) and propyl 4-hydroxybenzoate (0.2 g) were dissolved in boiling water (500 ml) for injection. After cooling to about 50°C there were added while stirring lactic acid (4 g), propylene glycol (0.05 g) and the A.I. (4 g). The solution was cooled to RT and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Claims

1. A compound of formula



(I)

a N-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

n is 0, 1 or 2;

m is 1 or 2, provided that if m is 2, then n is 1;

=Q is =O or =NR^3;

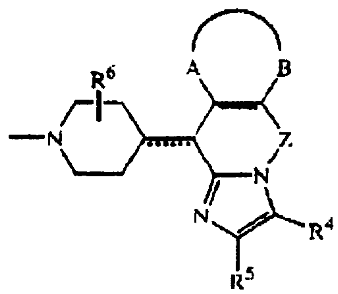
X is a covalent bond or a bivalent radical of formula -O-, -S-, -NR^3-;

R^1 is Ar^1, Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, wherein each C_{1-6}alkyl group is optionally substituted with hydroxy, C_{1-4}alkyloxy, oxo or a ketalized oxo substituent of formula -O-CH_2-CH_2-O- or -O-CH_2-CH_2-CH_2-O-;

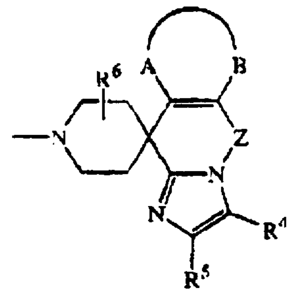
R^2 is Ar^2, Ar^2C_{1-6}alkyl, Het or HetC_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

L is a radical of formula



(a-1) or



(a-2);

wherein the dotted line is an optional bond;

each -A-B- independently is a bivalent radical of formula

-Y-CR^7=CH- (b-1);

-CH=CR^7-Y- (b-2);

-CH=CH-CH=CH- (b-3);

-CH=CR^7-CH=CH- (b-4);

-CH=CH-CR^7=CH- (b-5); or

-CH=CH-CH=CR^7- (b-6);

wherein each Y independently is a bivalent radical of formula -O-, -S- or -NR^8-;

each R^7 independently is C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl; carboxyl or hydroxycarbonylC_{1-6}alkyl; or

R^7 is hydrogen in case -A-B- is a radical of formula (b-1) or (b-2);

R^8 is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

each Z independently is Z^1 or Z^2;

wherein Z^1 is a bivalent radical of formula $-CH_2-$, $-CH_2-CH_2-$ or $-CH=CH-$; provided that when L is a radical of formula (a-1) and the dotted line is an extra bond, then Z^1 is other than $-CH_2-$;

Z^2 is a bivalent radical of formula $-CH_2-CHOH-$, $-CH_2-O-$, $-CH_2-C(=O)-$ or $-CH_2-C(=NOH)-$, provided that the $-CH_2-$ moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring;

each R^4 independently is hydrogen; C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl or carboxyl;

each R^5 independently is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, Ar^1 or halo; or

R^4 and R^5 taken together may form a bivalent radical of formula $-CH=CH-CH=CH-$ or $-CH_2-CH_2-CH_2-CH_2$;

each R^6 is hydrogen, C_{1-6}alkyl or Ar^1C_{1-6}alkyl;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or haloC_{1-4}alkyloxy;

Ar^2 is naphtalenyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkyloxy, haloC_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl and mono- or di(C_{1-4}alkyl)-aminocarbonyl; and

Het is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl.

2. A compound according to claim 1 wherein Het is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl,

benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl.

3. A compound according to claim 1 or 2 wherein R^1 is Ar^1C_{1-6}alkyl, R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl, X is a covalent bond and =Q is =O.

4. A compound according to any one of claims 1 to 3 wherein R^1 is phenylmethyl; R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl; n, m are 1; X is a covalent bond; and =Q is =O.

5. A compound according to any one of claims 1 to 4 wherein L is a radical of formula (a-1) wherein -A-B- is a radical of formula (b-1) wherein Y is -S-; and R^7 is hydrogen; or -A-B- is a radical of formula (b-2) wherein Y is $-NCH_3-$; and R^7 is hydrogen; or -A-B- is a radical of formula (b-3); Z is a bivalent radical of formula $-CH_2-$ or $-CH_2-CH_2-$, provided that when the dotted line is an extra bond, then Z is other than $-CH_2-$; R^4 is formyl; and R^5 is hydrogen; R^6 is hydrogen; or L is a radical of formula (a-2) wherein -A-B- is a radical of formula (b-3); Z is a bivalent radical of formula $-CH_2-CH_2-$; R^4, R^5 and R^6 are hydrogen.

6. A compound according to claim 1, wherein the compound is
1-[3,5-bis(trifluoromethyl)benzoyl]-4-(5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-1-yl)-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,9,10-tetrahydro-imidazo[1,2-a]thieno-[2,3-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]-pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine; and
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(3-formyl-5,6-dihydro-11*H*-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;
4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; and
4-[4-(5,6-dihydro-6-oxo-10*H*-imidazo[1,2-a]thieno[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; a stereoisomeric form, or a pharmaceutically acceptable acid addition salt thereof.

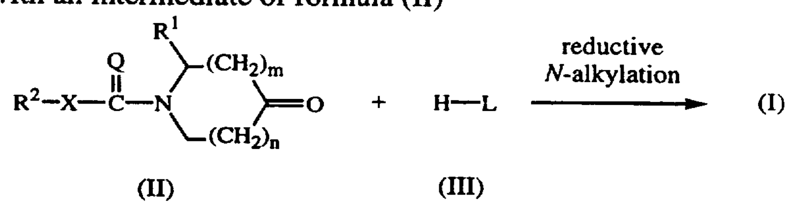
7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 6.

8. A process of preparing a composition as claimed in claim 7, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as described in any one claims 1 to 6.

9. A compound as claimed in any one of claims 1 to 6 for use as a medicine.

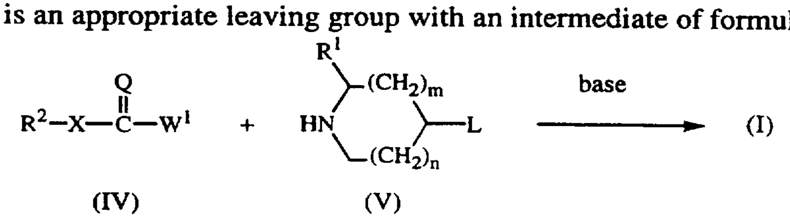
10. A process of preparing a compound as claimed in claim 1, characterized by,

a) reductively *N*-alkylating an intermediate of formula (III) wherein L is defined as in claim 1, with an intermediate of formula (II)



wherein R^1, R^2, X, Q, n and m are defined as in claim 1, in a reaction-inert solvent, in the presence of a reducing agent and optionally in the presence of a suitable catalyst;

b) reacting an intermediate of formula (IV) wherein R^2, X and Q are defined as in claim 1 and W^1 is an appropriate leaving group with an intermediate of formula (V)



wherein R^1, L, n and m are defined as in claim 1, in a reaction-inert solvent and in the presence of a suitable base;

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05885

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/20 C07D487/04 C07D471/04 C07D498/04 C07D495/14
C07D487/14 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 518 435 A (JANSSEN) 16 December 1992 see claims; tables 1-5	1,7-10
A	EP 0 518 434 A (JANSSEN) 16 December 1992 cited in the application see claims; tables 1-3	1,7-10
A	WO 95 02600 A (JANSSEN) 26 January 1995 cited in the application see the whole document	1,7-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1997	17.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Francois, J

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